Medical Information

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Clindamycin — Efficacy and Toxicity

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CLINDAMYCIN (CLEOCIN®), a member of the lincomycin group of antibiotics, is the 7-chloro-7-deoxy derivative of the parent compound lincomycin. The lincomycins are chemically unrelated to other antibiotics. Lincomycin, the first member of the group introduced for clinical use, has a spectrum and mechanism of action quite similar to that of erythromycin, and seemed to offer no clearcut advantage over the latter drug.[1] Clindamycin was found to have greater *in vitro* activity than lincomycin against some Gram-positive organisms, and to yield higher and more predictable serum levels than the parent compound;[2,3] it was therefore felt to be a more effective agent.

Although even early studies suggested no distinct advantage over other available agents in the treatment of Gram-positive infections,[4] nevertheless clindamycin has been suggested as a possible drug of choice in Group A beta-hemolytic streptococcal infection in all patients[5] or in patients allergic to penicillin,[6] and as an alternative when penicillins cannot be used in otitis media[7] and bacterial pneumonia.[8] Clindamycin has been suggested as a possible choice for the initial treatment of pneumonia thought to be secondary to Gram-positive bacteria or Mycoplasma pneumoniae infection,[9] although another study failed to show an effect of this agent on Mycoplasma pneumoniae pneumonia.[10] Indications listed in the 1974 *Physicians' Desk Reference* include upper and lower respiratory, skin and soft tissue streptococcal and staphylococcal infections, and upper and lower respiratory pneumococcal infections, as well as dental infections due to susceptible organisms.[11] It is presumably for the treatment of such conditions that physician prescription of clindamycin has increased dramatically, although increased usage of a variety of antibiotics seems to be a national trend.[12]

Clindamycin has gained such widespread physician acceptance that it is now one of the one hundred most often prescribed drugs in the United States. Data from The Queen's Medical Center in Honolulu (Table 1) illustrate the pronounced increase in the use of clindamycin since the introduction of the oral (1970) and parenteral (1973) preparations. Although clindamycin clearly may be effective in the therapy of a number of the infections referred to above, there are no data to show its superiority over other older agents of proven efficacy and safety, and lower cost.

Staphylococcus Aureus Infections

A clearer role for clindamycin has been shown in two types of infection. The first of these is in the therapy of infections caused by Staphylococcus aureus. Laboratory and clinical evidence of the efficacy of clindamycin against this organism has been published although the number of cases reported is not great.[13-15] Most strains of this species are inhibited by 0.1 microgram (μg) per ml of clindamycin; serum levels 50 to 100 times this are readily attained. For the first six months of 1974, susceptibility to clindamycin of all isolates of Staphylococcus aureus from our clinical laboratory by a standardized disc method[16] ranged from 94.6 to 100 percent.

The author has treated four patients with severe staphylococcal infection (two with endocarditis; one with facial cellulitis, bacteremia and pneumonia; one with bacteremia and multiple septic joints) with clindamycin because of intolerance to

TABLE 1.—*Yearly Volumes of Clindamycin Dispensed by the Pharmacy at The Queens Medical Center**

Year	*Oral (150mg tablets)*	*Parenteral (vials)*
1970†	3,840	..
1971	2,600	..
1972	4,200	..
1973	7,200	1,539
1974‡	21,400	6,326

*Data supplied by Ms. Nellie Chang, Director of Pharmacy, The Queen's Medical Center.

†Based on a five month period, adjusted to one year.

‡Based on a six month period, adjusted to one year.

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other antistaphylococcal agents. In one patient with endocarditis, the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) for clindamycin were 0.1 μg per ml and 3.12 μg per ml respectively, and serum bactericidal activity was present at a 1:8 dilution 30 minutes after a 600 mg infusion. In the second endocarditis case, the MIC and MBC for clindamycin were 0.05 μg per ml and 1.56 μg per ml respectively. Serum bactericidal activity was not measured.

The first patient responded clinically to clindamycin, but bacteriologic cure could not be determined as the drug had to be discontinued because of the development of a rash. In the second patient, a rash developed shortly after starting the drug, and thus therapeutic effect could not be determined. The third patient completed a four-week course of clindamycin and was in good health when last seen approximately four months after discharge from the hospital. The fourth patient's blood was sterilized, but the patient died from underlying disease. Thus, clindamycin appears to be a reasonable alternative drug for severe staphylococcal infection in patients who cannot tolerate penicillins or cephalosporins or whose organism is resistant to these. Clindamycin or vancomycin could be used in such patients although it should be noted that neither of these agents passes readily into the cerebrospinal fluid.

Bacteroides Fragilis Infections

A large amount of literature has appeared in recent years indicating the importance of anaerobic bacteria as pathogenic agents in infections. However, misconceptions regarding such organisms appear to be common. When considering anaerobic pathogens, one must recognize that there are anaerobic Gram-positive cocci (for example, Peptococcus and Peptostreptococcus), anaerobic Gram-negative cocci (for example, Veillonella), anaerobic Gram-positive rods (for instance, Clostridium) and anaerobic nonspore-forming Gram-negative rods—the latter often referred to collectively, though incorrectly, as Bacteroides. Penicillin is very active against almost all strains of the first three groups, and is the drug of choice when one (or more) of these organisms is recovered from a clinical specimen.[17] A number of other agents, including clindamycin, can be used if the patient is allergic to penicillin or if there is simultaneous infection with a penicillin-resistant anaerobe.

There is still disagreement as to the proper classification of the nonspore-forming anaerobic Gram-negative rods,[18] and a new classification has been proposed.[19] These organisms belong to the family Bacteroidaceae, and the term Bacteroides should be reserved for only members of that genus. Speciation is important clinically for the following reasons. First, Bacteroides fragilis is the predominant member of the family in the gastrointestinal flora,[20] is part of the normal flora of the female genital tract[21] and is commonly found in infections originating in these sites, while other Bacteroidaceae predominate in infections originating in the oropharynx.[22] Second, while most Bacteroides fragilis strains are resistant to penicillin, most other species of Bacteroides (B. oralis, B. melaninogenicus) and almost all Fusobacterium species are susceptible to clinically attainable levels of penicillin.[23]

It is often difficult to evaluate the efficacy of antimicrobial therapy of anaerobic infections, as the infections are frequently polymicrobial—with aerobes as well as a variety of anaerobes being involved. Additionally, adjunctive therapy such as surgical drainage of an abscess or removal of necrotic tissue may be the most important therapeutic measure. Nevertheless, two studies[18,24] have shown that at least in certain groups of patients with Bacteroidaceae bacteremia, treatment with a drug to which the organism is susceptible *in vitro* results in a pronounced reduction in the mortality rate. There is now a large volume of laboratory[25-28] and clinical[18,24,29-33] data demonstrating the efficacy of clindamycin in the treatment of infections caused by the nonspore-forming anaerobic Gram-negative bacilli, and the author's clinical experience is in agreement with these data. On the other hand, no studies have shown that clindamycin is more effective clinically than other drugs to which the organism is susceptible *in vitro*. As already noted, anaerobic infections originating in the oropharynx are usually susceptible to penicillin, and in certain clinical settings Gram-positive anaerobes predictably susceptible to penicillin may predominate.[34] Additionally, certain species of Clostridium may be resistant to clindamycin.[35] Thus, one cannot select therapy for an anaerobic infection generally, but must consider which anaerobes are likely to be involved.

When considering the indications for use of a new drug, major considerations include three questions: (1) Is the new agent more effective than older agents? and (2) Is it less toxic than

older agents? and (3) Is it equivalent in efficacy and toxicity, but less expensive? As has been noted, there is no evidence that clindamycin is more efficacious than other agents to which the organism is susceptible. One must always be cautious of unrecognized toxicity of new drugs, and this will be discussed in more detail later. Regarding cost, clindamycin is considerably more expensive than penicillin, and also than most other agents which may be used in the treatment of anaerobic infections.[36] Therefore, usage of clindamycin in anaerobic infections should be limited to serious infections where Bacteroides fragilis is suspected or has been proven to be a pathogen. These will be mainly cases where the gastrointestinal tract or female genital tract are the probable portals of entry. Treatment may justifiably be started on suspicion of B. fragilis, as anaerobic cultures require more time for growth than do aerobic cultures, and even in the best of circumstances, some false-negative cultures can be expected. Once an organism has been isolated and susceptibility testing done by a standardized method,[37] then one can choose from the agents to which the organism is susceptible.

Clindamycin-Related Colitis

While gastrointestinal intolerance and particularly diarrhea were well-known side effects of lincomycin, a lower incidence of these adverse reactions with clindamycin was stressed as a feature of the newer derivative.[38,39] Many clinical studies of the efficacy of clindamycin emphasized the lack of toxicity, particularly with regard to the gastrointestinal tract.[2,4-7,13-15,29-31,38,40] Among the gastrointestinal side effects noted relatively early in clinical studies with lincomycin was a syndrome resembling acute ulcerative colitis with fever, leukocytosis, abdominal pain and severe diarrhea, sometimes with blood and mucus in the stool.[41,42] In spite of case reports attributing this pseudomembranous colitis to lincomycin,[43,44] little attention was given to this syndrome over the next few years, presumably because gastrointestinal complications, including occasional cases of an identical syndrome, are recognized as complications of a variety of antibiotics.[45,46]

The occurrence of this syndrome following the administration of clindamycin was not reported until Cohen and co-workers[47] described three cases and alluded to another three they had seen. A subsequent article describing seven cases of pseudomembranous colitis associated with lincomycin[48] was followed by a number of letters to the editor[49-57] and case reports[58-64] which have shed light on the epidemiology of, and illustrated the clinical features of, the clindamycin-associated illness. Of the patients described in references 47 and 49 through 64 (patients in reference 62 are not included, as they are also described in reference 63), 25 are described in sufficient detail to extract the clinical information presented in Table 2.

The clinical features include relatively sudden onset of fever, abdominal pain and sometimes distention, and severe diarrhea—often with blood or mucus or both in the stool—occurring most often during but not infrequently after a course of clindamycin. This is most often seen with orally administered clindamycin, but may occur with intravenous administration of the drug as well. Although the manufacturer has felt that the occurrence of colitis is unrelated to the occurrence of simple diarrhea during treatment,[51] such diarrhea during treatment did occur in two of three patients in whom colitis developed after the course of clindamycin had been completed. In the other three patients with similarly timed onset of colitis, no mention is made of the presence or absence of diarrhea during therapy, though in one patient diarrhea and cramps had previously developed in relation to a course of lincomycin.[64]

TABLE 2.—*Clinical Features of 25 Cases of Clindamycin-Related Colitis*

	Number of Patients
Temporal relation of onset of colitis to clindamycin therapy	
During treatment	19
After treatment	6
Route of administration of clindamycin	
Oral	21
Intravenous	3
Not stated	1
Course of colitis	
Single episode	23
Recurrent disease	2
Corticosteroid therapy	
Not required, or required for less than one month	22
Required for longer than one month	3
Colectomy	
Not required	24
Required	1
Death directly related to colitis	
Did not occur	21
Occurred	4

The possibility that the colitis may be aggravated by opiates or their derivatives[51] is supported by several of the cases reported in the literature. Particularly grave features of the illness include the possibility of recurrent colitis,[54,64] the necessity for prolonged corticosteroid treatment,[47,50,54] the necessity for colectomy[56] and the possibility of death from toxic megacolon,[49] from persistent colitis[55,60] or from complications of treatment.[58]

The typical sigmoidoscopic appearance includes an erythematous mucosa which may be friable or edematous, and numerous white or yellowish raised plaques less than 1 cm in diameter.[61,62] Histologic features of the rectosigmoid include the presence of a pseudomembrane, surface ulceration and mucosal inflammation.[61,62] These histologic features are identical to those seen in other cases of pseudomembranous colitis, including both those associated with administration of antibiotics and those attributable to other causes.[44] Barium enema examination of the colon shows extensive involvement of the colon with innumerable small plaques as described on sigmoidoscopy. These are slightly raised above the surface of the mucosa and are particularly well shown on air contrast studies.[62,63] Ulceration may or may not be prominent.[64] Discontinuation of clindamycin may result in cessation of symptoms in those patients who develop colitis while taking the drug. Otherwise, symptomatic treatment, if necessary including rectal and sometimes systemic corticosteroids, usually results in clinical improvement. Opiates, however, should probably be avoided.

The incidence of clindamycin-related colitis is unknown. The manufacturer suggests that "serious colitis probably occurs at an overall rate of between one in 50,000 and one in 100,000 uses of clindamycin" (Letter, The Upjohn Company, August 16, 1974). The number of cases reported in the literature and presented at meetings suggests that the actual number may be considerably greater than this. While the incidence of this illness following use of other antibiotics is also known, the syndrome appears to be considerably more common after use of the lincomycin group of drugs.

Conclusion

Clindamycin is clearly an effective antimicrobial agent. It is particularly useful as an alternative agent to penicillins and cephalosporins in infections due to Staphylococcus aureus and in the management of infections due to nonspore-forming anaerobic Gram-negative bacteria, particularly Bacteroides fragilis. As with any new drug, adverse effects become more apparent with more extensive use of the drug. Clindamycin has replaced chloramphenicol as the drug of choice in severe Bacteroidaceae infections because of the bone marrow toxicity of chloramphenicol. A review of the literature suggests that severe adverse reactions may not be uncommon with clindamycin. The indications for the use of this drug are quite narrow. Its use in treating mild infections, or severe infections for which drugs of proven efficacy and safety are also available, is to be deplored. Clinicians and radiologists should be familiar with the clinical features of clindamycin-related colitis, and a history of current or prior treatment with clindamycin should be elicited in the evaluation of patients with diarrhea.

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